Kidney International, Vol. 18 (1980), pp. 207–220

Effect of pregnancy in patients with lupus nephropathy

JOHN P. HAYSLETT and ROBERT I. LYNN

Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Systemic lupus erythematosus (SLE) occurs primarily in women during child-bearing years. The possible influence of pregnancy on the underlying activity of SLE has important implications for this group of patients because of the threat of severe, and even life threatening, exacerbations of disease, and the possibility of a reduced likelihood of a successful outcome for the product of conception. On the basis of previous reports on large series of cases, the relationship between SLE and pregnancy is controversial [1–4]. Furthermore, although renal involvement is a common feature of SLE and is a major source of morbidity and death [5], the influence of pregnancy on lupus nephropathy has not been ascertained. Previous reports on the relationship between lupus nephropathy and pregnancy are difficult to analyze because, in general, few have detailed information on the chronologic sequence of nephropathy and pregnancy, and the type and severity of the underlying renal histopathologic lesion [1–3, 6–11]. Moreover, in some initial reports, current modes of treatment were not available.

The present study was undertaken to characterize the clinical course of SLE in patients with lupus nephropathy during pregnancy and postpartum. Because it seemed unlikely that sufficient clinical materials for analysis would be available to any single clinic, or that a prospective study of pregnancy in patients with SLE would be performed in the near future, we conducted a survey of nephrologists with an interest in lupus nephropathy, representing a wide geographic distribution.

This analysis is derived from data obtained on 65 pregnancies by 47 patients with SLE reported from 13 centers. All patients manifested clinical signs of lupus nephropathy at some time during the course of their illness, and renal biopsy material was available in 77% of cases. Because lupus nephropathy increases the morbidity associated with SLE, it seems likely that any bias in selection of these cases would favor those with greater severity. In addition, because these cases were obtained from multiple centers, the clinical material used in this analysis tends to reflect the widely divergent attitudes towards SLE and treatment modalities used to treat this disease.

Methods

The survey was performed by sending a letter of inquiry to 46 nephrology centers and individual nephrologists with an interest in lupus nephropathy, which asked each addressee whether he had detailed information on one or more patients with SLE during pregnancy that could be shared with the survey. A detailed questionnaire was subsequently sent to 22 individuals who returned a positive response. The questionnaire requested information in the following areas:

(1) Onset of SLE. Information was requested on the date and age of patients at onset of SLE and initial clinical manifestations, including signs of renal involvement, urine analysis, serum creatinine, creatinine clearance, and quantitative protein excretion. In addition, the results of the following tests were requested: LE test, complement levels (total hemolytic, C_3, and C_4), DNA antibody test, and antinuclear antibody tests. Each respondent was asked to provide the range of normal values for his laboratory. Information on the date and results of renal biopsy was obtained and included a detailed description of findings by light and electron microscopy and immunofluorescent microscopy. Last, we requested information on the use of drug therapy and the response to treatment.

(2) Pregnancy. The following information was asked about each pregnancy during three intervals (6 months prior to conception, during pregnancy, and 3 months following pregnancy [postpartum]):

Received for publication February 15, 1980

0085–2538/80/0018-0207 $02.80

clinical manifestations, including renal status, serologic parameters (as above), treatment, and response to treatment. In addition, data were obtained on the status of the product of conception, medical complications at time of delivery, and mode of delivery.

(3) Followup course. Information was obtained on clinical manifestations since last delivery, renal status, and serologic parameters. Recordings of subsequent specific renal findings were made. Finally, each respondent was asked to provide comments on the overall assessment of the relationship of SLE to pregnancy for each individual patient.

The source of data for the survey is listed below and indicates that they were obtained from 13 separate centers that returned completed questionnaires. In this analysis the following criteria and definitions were used:

Definition of SLE. Patients were included when signs and symptoms of disease and laboratory results conformed to the diagnostic criteria established by the American Rheumatology Association [12].

Extrarenal manifestations. Signs of systemic and multisystem disease ascribable to SLE were classified as mild, moderate, or severe. *Mild* severity was defined as manifestations that did not limit patient activity. *Moderate* severity limited physical activity to some degree, and *severe* activity described patients who were acutely ill and required hospitalization.

Renal status. A serum creatinine value of 1.5 mg/dl or more indicated overt renal insufficiency, and a protein excretion of > 300 mg/day was considered abnormal. The nephrotic syndrome was defined as a urine protein excretion > 3.0 g/day and a serum albumin < 3.0 g/dl.

Serologic parameters. Serologic parameters were classified as abnormal when the results of at least two different studies (complement, DNA antibody, and antinuclear antibody titer) exceeded the normal range of values.

Renal biopsy. The histopathologic classification of renal lesions used in this analysis has been previously reported by our laboratory [13], and is a modification of the Comerford and Cohen classification [14]:

Type I is normal glomerular structure or a mild proliferative lesion with no electron-dense deposits found on ultrastructure examination. *Type II* is a thickened capillary basement membrane with electron-dense deposits located in subepithelial loci; mesangial deposits are also usually present. *Type III* is a focal or diffuse proliferative glomerulonephritis of moderate or severe intensity, with subendothelial electron-dense deposits. Mesangial and occassionally subepithelial deposits may also be present. This type of lesion is often associated with exudation and focal areas of necrosis. *Type IIIa* is a mild to moderate proliferative glomerulonephritis with electron-dense deposits confined to the mesangial area.

Exacerbation is defined as the appearance of clinical extrarenal manifestations and/or signs of renal disease following a period of remission, or an increase in severity of extrarenal and/or renal manifestations in a patient with signs of disease activity. An increase in extrarenal manifestations occurred when severity changed from mild to moderate, or from moderate to severe, whereas an increase in renal manifestations was defined as a rise in the serum creatinine concentration of at least 0.5 mg/dl and/or an increase in urine protein excretion of 1.0 g/day.

Remission is complete absence of clinical signs or symptoms of disease activity.

Status of product of conception is as follows: *full-term delivery,* duration of pregnancy estimated to be 37 or more weeks; *abortus*, delivery before viability (< 500 g or < 21 weeks gestation); *premature,* delivery before 37 weeks gestation; *stillbirth,* fetal death after stage of viability was achieved (> 500 g or > 21 weeks gestation).

Results

This analysis was performed on clinical data obtained from 13 centers on 65 pregnancies by 47 patients. The onset of SLE occurred during pregnancy or postpartum in 9 pregnancies (14%). In the remaining 56 pregnancies, gestation occurred after onset of SLE, and in these pregnancies clinical manifestations of lupus nephropathy preceded conception in 80%. One or more renal biopsies were performed in 36 patients (77%). The average age at onset of SLE was 20.4 years, and the mean duration of followup from onset of disease was 8.9 years.

The clinical activity of SLE during a pregnancy and 3 months postpartum is shown in Table 1. These data demonstrate that the clinical course of SLE was not adversely influenced by pregnancy in 34 pregnancies (61%) antedated by onset of SLE. In 22 pregnancies (39%), an exacerbation, either relapse or worsening of disease activity, occurred during gestation or postpartum. In contrast to previous reports, exacerbation was more common during pregnancy than it was immediately following delivery [1, 8].

Analysis of pregnancies occurring after onset of SLE. Because previous reports suggest that the activity of SLE immediately before and at onset of pregnancy had an important influence on the course of disease during gestation and postpartum [1, 4, 11], individual pregnancies were classified as either exhibiting *(1)* complete clinical remission or *(2)* signs of *clinical activity,* during the 6-month interval before conception. In this classification, *clinical activity* was defined as any evidence of renal or multisystem disease. Serologic changes were not used as a criterion of clinical activity.

(1) Remission before pregnancy. There was no evidence of disease activity within 6 months of conception in 31 pregnancies, and as shown in Table 2, remission was sustained in 21 instances (68%). In 10 pregnancies (32%), an exacerbation occurred either during gestation (6) or postpartum (4). The outcome of the product of conception in this group is also shown in Table 2. After exclusion of pregnancies that were surgically interrupted, solely because of the presence of SLE and not because of a pregnancy-associated complication, the incidence of live births was 88%. Premature births did not exceed the expected rate of 8.2% recorded in a population of healthy subjects [15]. Of the 3 spontaneous abortions, 2 of these, occurring at 20 and 24 weeks, respectively, represent a fetal loss above the expected rate [16]. Overall, therefore, the likelihood of a successful outcome of pregnancy in patients in remission at onset of gestation was reduced about 8% (2/24), and fetal deaths occurred exclusively in patients who exhibited sustained remission. The rationale for surgical interruption in this group of pregnancies, as well as in other parts of the study, was concern for the possible adverse effect of pregnancy on SLE or possible harmful effects of cytotoxic agents. The activity of SLE was not adversely affected by therapeutic abortions, as previously suggested [1].

A summary of clinical data and renal biopsy results in individual patients is shown in Table 3. Serologic studies were performed before conception in approximately one half of the group and, as noted in Methods, were classified as abnormal when the results of at least two tests (antinuclear

Table 1. SLE activity during pregnancy and 3 months postpartum

Status of SLE during pregnancy and postpartum	Total
Unchanged	
Sustained remission	21
Active throughout	10
Exacerbation at pregnancy	
From remission at onset of pregnancy	6
From activity at onset of pregnancy	10
Exacerbation at 3 months postpartum	
From remission at onset of pregnancy	4
From activity at onset of pregnancy	2
Remission from activity at onset of pregnancy	
During pregnancy	3
During 3 months postpartum	0
First onset of SLE	
During pregnancy	6
During 3 months postpartum	3
Total	*65*

Table 2. Effect of SLE activity 6 months before conception on clinical course during pregnancy and postpartum, and on outcome of pregnancy

SLE in remission prior to conception		SLE clinically active prior to conception	
Remission sustained	Total	Severity unchanged	Total
Full-term deliveries	12	Full-term deliveries	6
Spontaneous abortion	3	Spontaneous abortion	2
Therapeutic abortion	6	Therapeutic abortion	1
Total	*21*	Still birth	1
		Total	*10*
Exacerbation at pregnancy or postpartum		Exacerbation at pregnancy or postpartum	
Full-term delivery	8	Full-term delivery	7
Premature delivery		Premature delivery	
Live	1	Live	0
Dead	0	Dead	1
Spontaneous abortion	0	Spontaneous abortion	0
Therapeutic abortion	1	Therapeutic abortion	1
Stillbirth	0	Stillbirth	3
Total	*10*	*Total*	*12*
		Remission at pregnancy	
		Full-term delivery	1
		Spontaneous abortion	1
		Therapeutic abortion	1
		Total	*3*

Table 3. Summary of clinical data of women with SLE in remission prior to conception[a]

Patient[b]	Past history		Onset preg.	6 Months before pregnancy				
	Manifestations	Rx		Manifestations	Serology	BUN/Creat. *mg/dl*	Urine prot. *g/day*	Rx
				Sustained remission				
1 (2)	Moderate extrarenal	Pred	2/67	None	—	15/—	<0.3	Pred
5	Moderate extrarenal hematuria	Pred Mustard	6/76	None	Inact	—/1.0	<0.3	Pred
8 (1)	Severe extrarenal	Pred	7/75	None	Act	—/0.7	<0.3	Pred
(2)	Prot. 1 to 2+		10/76	None	—	—/0.8	<0.3	Pred
15 (2)	Moderate extrarenal Prot. 2 to 3+	Pred	1/71	None	—	—/0.8	<0.3	None
18 (2)	Moderate extrarenal	Pred	12/74	None	Act	0/0.9	0.2	Pred
(3)	Prot. 2+		5/77	None	Inact	—	<0.3	Pred
20 (2)	Moderate extrarenal Prot. 2 to 3+	None	1/78	None	—	—	—	None
21 (2)	Moderate extrarenal	ACTH	7/65	None	—	—/1.0	1 to 2+	None
(3)	Nephrotic		12/66	None	—	—	—	Pred
22	Moderate extrarenal Prot. 0.8 g/day	Pred	6/67	—	—	—	—	None
29 (1)	Moderate extrarenal	Pred Imur	2/71	None	Inact	14/—	<0.3	Pred Imur
(2)	Prot. 3.2 g/day		/74	None	Inact	15/—	<0.3	
37	Moderate extrarenal Prot. 1.1 g/day	Pred Imur	11/75	None	Act	—/1.1	<0.3	Pred Imur
40 (1)	Moderate extrarenal	Pred Imur	6/70	None	Inact	—/0.7	<0.3	Pred Imur
(2)	Prot. 2.0 g/day		2/73	None	Inact	—/0.8	0.1	Pred
42	Moderate extrarenal Prot. 2+	Pred	9/61	None	—	—/1.0	1+	Pred
43	Mild extrarenal Prot. 2+	Pred Imur	11/74	None	Act	—/0.8	0.1	Pred Imur
45	Moderate extrarenal Nephrotic	Pred Imur	12/68	None	Inact	—/0.8	0.2	Pred Imur
49 (1)	Moderate extrarenal	Pred Imur	6/74	None	Inact	—/1.5	0.1	Pred
(2)	Prot. 2.0 g/day		4/77	None	Inact	—/0.8	0.1	Pred
				Exacerbation during pregnancy or postpartum				
2	Moderate extrarenal Prot. 2+	Pred Imur	9/72	None	—	—	<0.3	Pred
19	Severe extrarenal Creat. 4.2 mg/dl Prot. 0.6 g/day	Pred	7/71	None	Inact	—/1.5	0.2	Pred

Table 3 (*continued*)

During pregnancy and postpartum								
Manifestations	Serology	BUN/Creat *mg/dl*	Urine prot. *g/day*	BP *mm/Hg*	Rx	At delivery	Renal biopsy	Comment
				Sustained remission				
None	—	15/—	<0.3		Pred	FT	10/73 Type IIIa	1972–73 flare, proteinuria >1976, remission—1979
None	Inact	—/0.5	<0.3		Pred	FT	—	Complete remission 1979
None	—	—/1.0	<0.3		Pred	TA	—	
None	—	—/0.8	<0.3		Pred	TA	—	Complete remission 1979
None	—	0/0.8	<0.3		None	SA	1961 Type III	Subsequent flares
None	—	11/—	0.2		Pred	FT	8/73 Type III	
None	Act	—/0.8	0.4		Pred	FT		Complete remission 1979
None	—	—	—		None	SA	6/77 Type III	Apparent remission
None	Inact	—/0.8	0.7	140 85	None	FT	4/71-Type III 8/75-Type IIIa	
None	—	—/1.1	1+		Pred	TA		Creat, 1.6 mg/dl; prot. 0.8 g/day, 1975
None	—	—	—		None	SA	8/61 Type III 6/62 Type II 6/71 Type I	Complete remission 1977
None	Inact	14/—	<0.3		Pred Imur	FT	5/70 Type III	
None	Inact	15/—	<0.3		—	FT		Complete remission 1979
None	Act	—/0.6	<0.3	135 90	Pred Imur	FT	4/75 Type III	Complete remission 1977
None	Inact	—/0.8	0.1	110 60	Pred	FT	3/67 Type III	Complete remission 1979
None	Inact	—/1.0	0.1	115 60	Pred	FT	4/72 Type IIIa 1/74 Type IIIa 7/77—Type I	
None	Inact	—/0.9	1+		Pred	TA	10/70 Type III 8/75 Type IIIa	1967 Nephrotic, remission on Pred-Imur, complete remission, 1975
↑ BP	Act	—/0.8	0.1	140 100	Pred Imur	TA	6/74 Type III 1976 Type II	Persistent mild extrarenal 1979
None	Inact	0/0.8	<0.3	115 60	Pred Imur	TA	1/68 Type III 1/70 Type II	Renal failure 4 yr after pregnancy
None	Inact	—/0.9	0.1	120 70	Pred	FT	8/68—Type II 9/71—Type IIIa	
None	Inact	—/0.8	0.1	115 60	Pred	FT	9/73—Type I	Complete remission 1979
				Exacerbation during pregnancy or postpartum				
Nephrotic Renal failure	Act	—/>6.0	9.0	150 > 100	Pred Cytox	FT	5/73 Type IIIa	Relapse 3rd trimester, complete remission 1979
↑ BP	Inact	—/1.3	1.6	150 120	Pred	FT	4/71 Type I	Preeclampsia trimester, complete remission 1978

Table 3 (*continued*)

Patient[b]	Past history		Onset preg.	6 Months before pregnancy				
	Manifestations	Rx		Manifestations	Serology	BUN/Creat. *mg/dl*	Urine prot. *g/day*	Rx
				Sustained remission				
20 (3)	Moderate extrarenal Hematuria	None	2/79	None	—	—	—	None
21 (1)	Moderate extrarenal Nephrotic	ACTH	4/62	None	—	—	—	—
25 (2)	Moderate extrarenal Nephrotic Creat, 2.0 mg/dl	Pred	6/78	↑ BP	Inact	0/0.7	1+	None
38	Moderate extrarenal Prot. 1 to 2+	Pred	4/76	None	Inact	—	<0.3	Pred
17	Severe extrarenal	Pred	6/78	None	—	—/0.8	<0.3	Pred
50	Moderate extrarenal	Pred	8/68	None	—	0/1.0	<0.3	None
15 (1)	Moderate extrarenal Prot. 2 to 3+	Pred	5/64	None	—	—	—	None
48	Moderate extrarenal Prot. 1 yo 2+	Pred	5/69	None	—	12/—	0.1	None

[a] The following abbreviations are used; hx, history; preg, pregnancy; Bx, biopsy; Rx, treatment; BP, blood pressure; prot., urine protein; Creat., serum creatinine; Pred, prednisone; Imur, Imuran; chloro, chloroquin; Inact, inactive or normal values; Act, active or abnormal values; FT, full term delivery; SA, spontaneous abortion; TA, therapeutic abortion.

[b] The number in parenthesis following some of the case numbers indicates the order of pregnancies in women with multiple births.

antibody, complement, and DNA antibody) exceeded normal values. Inspection of Table 3 demonstrates that, in general, serologic parameters corresponded to clinical signs of disease activity. Among pregnancies characterized by sustained remission, clinical evidence of lupus nephropathy was present at an earlier stage of the disease in 20 of 21 cases, and included nephrotic syndrome in 2 cases and renal insufficiency in 1. In other cases, the presence of asymptomatic proteinuria or hematuria provided evidence of renal involvement. In 6 instances, a diffuse glomerulonephropathy with subendothelial deposits (type III) was found by renal biopsy 6 months or more before conception, and in 3 cases a typle III lesion was demonstrated within 6 months of pregnancy. In each of 8 cases in which additional renal biopsies were subsequently performed, there was histologic evidence of a reduction in the inflammatory response by light microscopy and transformation, by ultrastructure, to another histologic classification due to loss of subendothelial deposits. The initial renal biopsy revealed a type II and type I lesion before pregnancy in 2 patients, respectively, and 2 patients were shown to have a type IIIa lesion on biopsy performed during subsequent followup.

Among 10 pregnancies characterized by exacerbation during gestation or postpartum, there was previous evidence of renal disease in 8 and relapse involved signs of lupus nephropathy in all but one pregnancy, including 3 cases of renal insufficiency and 3 episodes of nephrotic syndrome. Although the blood pressure recordings were not available in all patients during pregnancy, hypertension occurred in at least 7 of 10 pregnancies. There were no patient deaths, and in the 8 cases followed for more than 3 months after delivery, there was a complete or partial reversal of the exacerbation. Renal biopsy was performed in 8 patients and provided adequate tissue for analysis in 7. In 2 patients, a type III lesion was found 6 months or more before conception; 1 of these patients developed nephrotic syndrome and renal insufficiency during pregnancy and was shown, by biopsy in the first trimester, to have chronic glomer-

Table 3 (*continued*)

	During pregnancy and postpartum							
Manifestations	Serology	BUN/Creat *mg/dl*	Urine prot. *g/day*	BP *mm/Hg*	Rx	At delivery	Renal biopsy	Comment
				Sustained remission				
Severe extrarenal Nephrotic Renal failure	Act	—/3.5	5.0		Pred	TA	6/77 Type III 4/79 Chronic GN	Exacerbation 1st trimester, 1 mo followup: Creat 1.6 mg/dl; urine prot., 7.0 g/day
↑ BP	Act	10/—	3.0	155 105	Pred	FT	8/62 Inadequate	Partial remission, Nephrotic syndrome 2 subsequent pregnancies
↑ BP	—	—/0.6	3+	150 > 100	None	FT	—	↑ BP and urine prot. in 3rd trimester, followup 3 mo.
Fever Arthritis Cerebritis	Act	—/4.3	1.0	150 105	Pred	Premature Alive	—	Persistent ↑ BP, Creat, 1.2 mg/dl, Urine prot. 0.7 g/day, 1979
Arthritis	Inact	0/0.5	0.7	150 > 100	Pred	FT	3/79 Type IIIa	Preeclampsia, onset proteinuria postpartum, complete remission 1979
None	—	0/1.0	1.2		None	FT	12/69 Type III	Exacerbation postpartum proteinuria and psychosis, complete remission 1974
Arthritis	—	—	—		Chloro	FT	1961 Type III	Mild flare postpartum
Arthritis	Act	—/0.8	2+	150 > 100	Pred	FT	3/70 Type I	Mild flare with proteinuria postpartum, mild nonrenal 1979

ulonephritis, whereas the other patient experienced only mild extra renal manifestations postpartum. A third patient exhibited proteinuria during gestation and was shown to have a type III lesion 8 months after delivery. Renal biopsies performed shortly before conception or immediately after delivery in 4 patients revealed a type IIIa lesion in 2 cases and type I histopathologic change in 2. Of these patients with a proliferative glomerulonephritis, of mild to moderate severity, the exacerbation involved mild proteinuria in 3, but in the fourth reversible renal failure and nephrotic syndrome occurred.

In summary, in the presence of complete clinical remission of SLE of at 6 months, the outlook for a live birth was reduced only slightly below the rate expected in the normal population. Although exacerbations occurred in 30% of pregnancies, significant morbidity occurred in only about 10% of these pregnancies, and in most patients there was a reversal of symptoms following delivery. It is important to emphasize that these results were observed in a group of patients with a 90% incidence of antecedent lupus nephropathy. Moreover, in 12 patients, renal biopsy revealed a type III glomerulonephropathy in the past history or near to the time of gestation.

(2) SLE clinically active prior to conception. In 25 pregnancies, there was evidence of disease activity in the 6-month interval before conception. Clinical manifestations remained unchanged in 10 (40%), improved in 3 (12%), and worsened in 12 (48%) during pregnancy and postpartum as shown in Table 2. In pregnancies associated with exacerbation, the increase in SLE activity was noted during pregnancy in 10 of 12 cases. The incidence of live births in this group of pregnancies was 64%, after exclusion of surgically interrupted pregnancies. In the remaining 8 pregnancies, fetal loss, either due to spontaneous abortion, prematurity, or stillbirth, was probably attributable to SLE activity or hypertension in at least 7 instances. In 1 pregnancy, the spontaneous abortion at 7 weeks' gestation was within the expected rate. Fetal loss due to SLE in this group of pregnancies, therefore, was approximately 32%. Significant hypertension was recorded in 8 of 25 pregnancies.

Clinical data and results of renal biopsy in individual pregnancies are shown in Table 4. Serologic

Table 4. Summary of clinical data of women with SLE clinically active prior to conception[a]

Patient	Past history		Onset preg.	6 Months before pregnancy				
	Manifestations	Rx		Manifestations	Serology	BUN/Creat *mg/dl*	Urine prot. *g/day*	Rx
				Sustained activity				
7	Severe extrarenal Nephrotic	Pred Imur	5/74	Nephrotic, mild activity	Act	—/0.6	7.0	Pred
14 (1)	Moderate extrarenal	Pred	7/74	Nephrotic	—	—/1.0	5.0	Pred
(2)	Nephrotic		2/79	None, BP 150/110	Inact	—4.0	1.0	None
16	Moderate extrarenal Nephrotic	None	1/65	Moderate activity	Inact	—/0.9	2+	Chloro
25 (1)	Moderate extrarenal Nephrotic Cr-2.0 mg/dl	Pred	9/69	BP 160/100	—	—/0.8	1.9	None
31	Moderate extrarenal Nephrotic	Pred	1/78	None	Inact	—/1.0	2+	Pred Imur
34	Moderate extrarenal Prot 1.0 g/d	Pred	4/78	Onset SLE	Act	—/1.3	1.0	Pred
35	Moderate extrarenal	Pred	5/77	Mild activity	Inact	—/0.8	<0.3	None
36	Severe extrarenal Nephrotic	Pred Imur	6/77	None	Act	—/0.8	3.0	Pred Imur
39	Rash Nephrotic	Pred Imur	2/78	None	Inact	—/1.4	1.3	None
				Exacerbation				
3	Mild extrarenal	Pred Imur	12/73	Mild activity	Act	—/0.9	<0.3	Pred
4	Moderate extrarenal Hematuria Prot 3.1 g/d	Pred	2/73	Moderate activity	—	—/1.0	—	Pred
9	Moderate extrarenal	Pred	12/73	Moderate activity	—	—/1.0	<0.3	None
10	Moderate extrarenal Nephrotic	Pred	5/73	Moderate activity	Act	—	1+	Pred
24	Mild extrarenal Prot 1.7 g/d	Pred Imur	4/71	None	Act	—/0.5	2+	None
13	Mild extrarenal	None	11/79	Mild activity	—	—/0.9	<0.3	None
15 (3)	Moderate extrarenal Prot 2-3+	Pred	10/77	Moderate activity	Inact	13/0.8	<0.3	None
28	Mild extrarenal	Pred	7/64	Onset SLE	Act	—	—	Pred
33	Mild extrarenal	Pred	2/76	None	—	—/2.0	—	Pred
41 (1)	Moderate extrarenal	None	7/70	Moderate activity	Act	—/1.3	<0.3	Pred
46	Severe extrarenal Nephrotic	Pred	5/65	Onset SLE	Act	—/1.2	4.4	Pred
6	Moderate extrarenal Prot 1.9 g/d	Pred Imur	3/74	Mild activity	Inact	—	—	Pred Imur

Table 4 (*continued*)

Pregnancy and postpartum								
Manifestations	Serology	BUN/Creat *mg/dl*	Urine prot. *g/day*	BP *mm/Hg*	Rx	Delivery	Renal BX	Comment
				Sustained activity				
Nephrotic	Inact	—/0.9	12.0	> 150/100	Pred	FT	6/69 Type II	Renal failure 1976, dialysis 1979
Nephrotic	—	—/1.0	4.0		Pred	TA	2/75	
None	Inact	—/3.5	2.5	135/100	None	SA	Type II	4 mo followup: Creat 3.8 mg/dl, prot. 1.4 g/day
Moderate activity	—	12/—	2+		Chloro	FT	3/62 Type II	Remission, BUN 8 mg/dl, Prot 1+, 1970
None	—	—/0.6	1.1		None	FT	—	Remission of proteinuria & subsequent preg.
None	Inact	0/0.7	0.4	> 150/100	Pred	FT	2/74 Type III 9/75 Type III	Persistent proteinuria, 1979
Moderate activity	Act	—/1.6	1.0		Pred	SA	6/78 Type II	Material death Adrenal failure
Mild activity	Act	—/0.9	<0.3		Pred	FT	5/79 Type IIIa	Onset proteinuria 12 mo. after delivery
None	Act	—/1.4	3+	130/90	Pred Imur	Stillbirth	1/76 Type III	1 mo. followup
None	Inact	—/0.6	0.4		None	FT	6/76 Type III	Persistent proteinuria, 1979
				Exacerbation				
Severe activity	Act	—/0.9	<0.3		Pred	TA	3/73 Type III 2/76 Type III	Mild activity: Creat 1.9 mg/dl, prot. 7.3 g/day, 1979
Nephrotic	Act	—/1.7	6.0		Pred Chloro	FT	1967 Type IIIa	Complete remission 1979
Nephrotic anemia	Act	—/1.6	13.5		Pred	FT	None	Persistent nephrosis 1979
Severe activity	Act	—/1.0	2.0		Pred Imur	FT	None	Persistent proteinuria 1979
Nephrotic	Inact	—/0.7	7.0		Pred	FT	None	Partial remission nephrosis 1979
Thrombo-cytopenia	Act	—/1.3	2.7	160/106	Pred	Stillbirth	None	Persistant activity, resolution of proteinuria 1979
Severe activity	Inact	—/0.8	<0.3		None	FT	1961 Type III	Remission 1978
Nephrotic	Act	60/—	6.0		Pred	FT	None	Remission 1979
Renal failure	—	—/6.9	2.0	230/130	Pred	Premature death	None	2 mo. followup
Severe activity	Act	—/0.6	0.1		Pred	Stillbirth	4/74 Type II	Transient prot 1974, remission 1979
Moderate activity	Act	—/22.0	>4.0	160/105	Pred	Stillbirth	2/65 Type III	Maternal death 4 mo. after delivery
Hypertension	—	0/0.9	0.5	166/108	Pred Imur	FT	11/72 Type II 11/75 Type II	Remission 1979

Table 4 (*continued*)

Patient	Past history		Onset preg.	6 Months before pregnancy				
	Manifestations	Rx		Manifestations	Serology	BUN/Creat *mg/dl*	Urine prot. *g/day*	Rx
				Remission				
1 (1)	Moderate extrarenal	Pred	1966	Onset SLE	Act	0/0.8	<0.3	Pred
27	Moderate extrarenal Nephrotic	None	11/71	None	Inact	—/0.5	1.1	None
47	Moderate extrarenal Prot 2+	Pred Imur	11/76	Mild activity	Inact	—/0.9	<0.3	Pred

[a] Abbreviations are defined in Table 3.

studies were performed in 19 patients before onset of pregnancy and, as in the previous group, corresponded in general with the presence and activity of SLE. Because there was a poor correlation between the results of serologic tests and the course of disease activity during pregnancy and postpartum, these studies did not provide a useful index for predicting the likelihood of exacerbation. Among the 10 pregnancies in which activity of disease remained unchanged throughout pregnancy and postpartum, a history of lupus nephropathy was present in 9, and included nephrotic syndrome in 8 (1 patient also had exhibited reversible renal insufficiency) and asymptomatic proteinuria in 1 patient. The single maternal death in this group of pregnancies was attributed to adrenal failure due to abrupt termination of glucocorticoid treatment. Renal biopsy was performed in 9 of 10 cases. Each of 3 patients with a type III lesion on biopsy 6 months or more before conception had persistent, and unchanged, proteinuria and normal renal function during pregnancy. Five pregnancies in 4 patients were associated with a type II lesion. Proteinuria, including nephrotic syndrome in 2 of these pregnancies, and renal function were not affected by pregnancy. Proteinuria first occurred approximately 1 year after delivery in 1 patient, and a type IIIa lesion was demonstrated by biopsy.

One half of the pregnancies associated with exacerbation exhibited signs of renal involvement before conception, and these included nephrotic syndrome in 2 patients and asymptomatic proteinuria in the remaining patients. Three patients experienced severe extrarenal signs of activity during or following pregnancy, and in 9 pregnancies, exacerbation was characterized by manifestations of lupus nephropathy, including nephrotic syndrome in 5 pregnancies; in 2 of these pregnancies renal failure also occurred. Renal biopsies were performed in 6 of 12 patients and revealed a type III lesion in 3, a type II lesion in 2, and in the remaining patient a type IIIa injury pattern. One maternal death was recorded in a patient with onset of SLE within 6 months of gestation and a progressively deteriorating course. In 11 patients followed beyond a few months after delivery, there was a reversal of the exacerbation, both of extrarenal and renal manifestations, in 8 instances.

Three patients demonstrated an amelioration of activity after onset of pregnancy; in 2 patients there were extrarenal signs of activity before conception, and in 1 patient proteinuria was present. Renal biopsy demonstrated a type III lesion prior to gestation in 1 patient and types III and IIIa in the other cases at a later time. Complete clinical remission persisted after delivery in all 3 patients.

In summary, the course of pregnancy was more problematic in cases with ongoing signs of activity through the time of conception. The likelihood of a live birth was approximately 65%, and there was nearly a 50% rate of exacerbation. Although exacerbation and hypertension tended to be more severe in these pregnancies than they were in the previous group, most patients experienced clinical improvement following delivery.

Onset of SLE during pregnancy or postpartum. The onset of SLE occurred during pregnancy or postpartum in 9 patients. A summary of these cases is shown in Table 5. Signs of lupus nephropathy were found at onset in 5 patients, but in the remaining 4 patients renal involvement became evident at a later time during followup. Excluding the single

Table 4 (*continued*)

Pregnancy and postpartum								
Manifestations	Serology	BUN/Creat *mg/dl*	Urine prot. *g/day*	BP *mm/Hg*	Rx	Delivery	Renal BX	Comment
					Remission			
None	—	0/0.7	<0.3		Pred	SA	10/73 Type IIIa	Remission 1979
None	Act	0/0.5	0.2		None	FT	3/74 Type III	Remission 1979
None	—	0/0.8	<0.3		Pred	TA	10/72 Type III 10/74 Type I	Remission 1978

therapeutic abortion, the incidence of live births was 63%. The rate of fetal loss due to the concurrence of SLE and pregnancy was approximately 25% (a still birth and 1 spontaneous abortion at 24 weeks). There was 1 death in this group of pregnancies, involving a patient who had persistent clinical activity and died of pancreatitis 18 months after delivery. Despite the relatively severe initial manifestations of SLE in the remaining patients, clinical remission occurred in 7 patients, and 5 had subsequent pregnancies. Renal biopsies were performed in all but 1 patient and revealed a type III lesion within 6 months of delivery in 5 patients. In 3 patients the underlying lesion was identified a year or more later, and demonstrated a type III lesion in 2 and a type IIIa lesion in 1 patient.

Discussion

The influence of pregnancy on the natural course of SLE and of SLE on the outcome of pregnancy have not been established. Although reports on small series of patients with SLE have tended to emphasize a high maternal complication rate during pregnancy and a reduced likelihood of a successful outcome for the product of conception [7, 9, 17], reports on large series, including a wider spectrum of disease severity, have not supported these conclusions [1–4]. Although it is clear from previous studies that patients with clinical evidence of active SLE at onset of gestation often experience a hectic course during pregnancy and postpartum [1, 4, 11], such occurrences have not been distinguished from the unpredictable natural course of active SLE.

Table 5. Onset of SLE during pregnancy or postpartum[a]

Patient	Onset preg.	Onset SLE	Extrarenal manifestations	BUN/Creat *mg/dl*	Urine protein *g/day*	BP *mm/Hg*	RX	Del.	Renal BX	Subsequent pregnancies
17	1/65	1st trimester	Heart failure	—/0.6	<0.3		Pred	TA	3/79, Type IIIa	3/79, mild exacerbation
18	12/62	Postpartum	Arthritis, fever lympha-denopathy	—/0.3	0.2		Pred	SA	8/73, Type III	12/74, FT, uncomplicated 5/77, FT, uncomplicated
20	12/76	Postpartum	Fever, pleuritis hematuria	—/3.7	12.0		None	SA	6/77, Type III 4/79, Type IIIa	1978, SA, uncomplicated 2/79, SA, uncomplicated, Creat, 3.5 mg/dl
23	6/62	2nd trimester	Abdominal pain, jaundice	—/1.0	2+	110	None	Premat. live	3/63, Type III	None, maternal death, 18 mo. due to pancreatitis
26	12/74	3rd trimester	Neophrotic	—/0.8	7.0		Pred	FT	1/75, Type III	None, complete remission 1979
27	7/73	2nd trimester	Nephrotic	—/1.7	10.0		Pred	Stillbirth	3/74, Type III	3/77, FT, uncomplicated
32	7/78	2nd trimester	Nephrotic, arthritis	—/1.5	9.0		Pred	FT	None	None, short followup
41	3/66	Postpartum	Arthritis	—/1.3	<0.3	150	None	FT	12/71, Type III 4/74, Type II	7/70, stillbirth, remission 1979
44	5/70	1st trimester	Arthritis, nephrotic	—/1.0	4.0		None	FT	5/71, Type III	None, partial remission 3 mo. postpartum

[a] Abbreviations are defined in Table 3.

Moreover, in regards to the contemporary management of patients with SLE, as modified by treatment, it is important to recall that in many of the initial reports on the relationship between SLE and pregnancy, treatment with glucocorticoids and/or cytotoxic agents were not routinely available or used [1, 2, 4, 8].

The relationship between pregnancy and lupus nephropathy is also unclear. Previous studies have indicated improvement, no change, or worsening in the course of lupus nephropathy during gestation [1–4, 6–11, 17–19]. There are few details, however, on the nature of the renal lesions, the time sequence between onset of renal disease and pregnancy, and the characteristics of renal function before onset of pregnancy. An evaluation of this relationship is also complicated by the potential influence of renal disease, itself, in the absence of SLE, on fetal development and normal physiologic changes of pregnancy.

The patients in this survey provide an important source of case material for evaluation of the effect of pregnancy on lupus nephropathy. In nearly 80% of subjects, the onset of lupus nephropathy antedated conception or occurred concurrently with gestation. In the remaining patients, renal involvement became clinically evident during a subsequent stage of their illness. In addition, information on the nature of the renal lesion was available in 77% of patients, and clinical manifestations of renal disease were moderately severe in the majority of cases. Before and/or during pregnancy, the nephrotic syndrome occurred in 26 patients, and overt renal insufficiency, on the basis of a serum creatinine value above 1.5 mg/dl, was present in a total of 13 subjects. It seems likely, therefore, that these patients represent a high-risk group for the potential of complications during pregnancy because of the concurrence of renal disease, as well as the presence of SLE.

It is clear from this analysis that neither SLE nor a history of lupus nephropathy exclude a successful pregnancy. Despite clinical evidence for antecedent renal disease in most patients in this series, and a high incidence of severe histopathologic changes by renal biopsy, the activity of SLE was apparently not influenced by pregnancy in nearly two thirds of the cases. Moreover, in pregnancies that occurred after the onset of SLE, including those immediately preceded by active SLE and/or persistent signs of lupus nephropathy, the rate of fetal wastage due to SLE was only approximately 20%.

Among the 56 pregnancies that followed the onset of SLE, an important determinant of the course of SLE during pregnancy and postpartum, and of the outcome of pregnancy, was evidence of complete clinical remission of at least 6 months' duration before conception. In these pregnancies, remission persisted in two thirds, severe reversible exacerbations occurred in 10%, and the rate of successful live births of 92% was comparable to that reported by Ferris [20] and Strauch and Hayslett [21] in normotensive gravidas with other diverse types of renal parenchymal disease. The occurrence of pregnancy in patients with ongoing signs of SLE activity and/or renal disease was associated with a more hectic course during pregnancy and postpartum, as expected, and a successful outcome was reduced by 25%. In this group of pregnancies, however, it seems likely that the recorded incidence of exacerbation overestimates to some extent the adverse effect of pregnancy on the course of SLE. It is possible, for example, that worsening of disease activity was consistent with the natural variation of disease activity in some patients, and that an increase in urinary protein excretion, classified as exacerbation, did not, in fact, reflect an increase in SLE activity or an intrinsic change in the renal lesion in all cases. Previous studies have suggested that the rate of protein excretion in patients with preexisting proteinuria may increase transiently during pregnancy without an alteration in the natural history of the renal disease [21]. In 5 of 12 pregnancies characterized by proteinuria during 6 months prior to conception and classified as exhibiting an exacerbation, protein excretion rose during pregnancy, in the absence of systemic activity, and remitted completely, or partially, after delivery. In summary, therefore, it seems likely that the calculated rate of exacerbation in patients with signs of SLE activity and/or renal disease immediately before conception overestimates the actual rate of change in activity of SLE.

In agreement with previous reports the onset of SLE during pregnancy or postpartum caused significant maternal morbidity and a fetal loss of approximately 37%. There was no evidence, however, that the subsequent course of the patients was different from the course expected in the absence of pregnancy, and 5 of 9 patients with this occurrence experienced subsequent uncomplicated pregnancies.

A total of 16 pregnancies were complicated by the nephrotic syndrome. It was of interest, therefore, to analyze these pregnancies independently of the associated SLE activity. If the single nonindicated induced abortion is excluded, there were 9 full-term live births among 10 nephrotic gravidas with a

serum creatinine value of 1.5 mg/dl or less. In contrast, there were only 2 successful outcomes among 5 uninterrupted pregnancies in patients with nephrotic syndrome and renal insufficiency. These data are in agreement with the analysis of Lindheimer and Katz [22] that indicates a good prognosis for the nephrotic syndrome in pregnancy, provided that hypertension is absent and renal function is adequate.

In a separate analysis of 10 noninterrupted pregnancies in patients with a serum creatinine value of 1.5 mg/dl or more, including patients with and without nephrotic syndrome, the fetal loss was 50%. Of the 5 live births in this group, it was of interest that the serum creatinine was 4.0 mg/dl or more during pregnancy in 3 patients, indicating that a successful outcome may occur occasionally despite severe renal failure.

An important interest in this study was the correlation of the renal lesion by biopsy with the clinical course during pregnancy. There is substantial evidence that subendothelial deposits (type III), an ultrastructural change usually associated with a more intense intraglomerular proliferative lesion, reflect a more aggressive form of lupus nephropathy compared with lesions with no deposits (type I), subepithelial deposits (type II), or deposits localized to the mesangial region (type IIIa) [23, 24]. In the present study, there were 18 patients with a type III lesion on the initial renal biopsy, performed either before gestation or postpartum. Renal insufficiency occurred in 2 of these patients. Under the same conditions, there were 6 patients with a type IIIa lesion, 7 with a type II pattern, and 3 with type I, and renal function remained normal in all patients. Following biopsy, with the exception of 2 patients, treatment was instituted in the form of prednisone alone or in combination with a cytoxic agent.

Although there was no apparent correlation between the type of renal lesion and the subsequent level of renal function, it is possible that the pattern of glomerular injury was changed, due to treatment, in patients with a type III lesion on the initial biopsy. A previous study by Hecht et al demonstrated a transformation from type III to lesions of the type I or type II variety in 20 of 31 patients treated with prednisone and azathioprine for at least 2 years [13]. In the present study, serial biopsies were performed in 10 patients with a type III lesion on the initial study. In these cases, there was a subsequent transformation to either type II, IIIa, or I in 7 patients, no change in 2, and a change to chronic glomerulonephritis without deposits in 1 patient. Renal biopsy was performed in 4 patients in whom SLE first occurred during pregnancy or postpartum, and a type III lesion was identified in all cases. Renal function was reduced in 2 patients and was normal in 2.

It seems likely, therefore, that the histopathologic pattern of injury found by biopsy in many patients in this series may not have represented the actual type of renal lesion during gestation, because the procedure was most often performed 6 months to several years before pregnancy. In our view, however, information derived from renal biopsy provides useful data in the assessment of the type and severity of renal involvement and should be used in the evaluation of patients with SLE who are considering the possibility of pregnancy. Future studies will be necessary to confirm the validity of this approach.

Finally, in this series of pregnancies and in each of the papers cited in this report, there is no evidence that use of glucocorticoids or cytotoxic agents induced developmental anomalies in the offspring of women treated during pregnancy, in agreement with the results obtained in patients with renal homografts treated with similar drugs [25]. Because complete suppression of SLE activity increases the likelihood of an uncomplicated pregnancy, appropriate treatment should not be withheld from women with SLE who become pregnant. The data available in this series of patients was inadequate to determine whether an increase in steroid therapy postpartum reduced the incidence of exacerbations after delivery or has a role in the management of patients with SLE.

Conclusion. The data indicate that a history of lupus nephropathy does not preclude an outlook for a successful pregnancy in patients with SLE. Complete clinical remission for at least 6 months indicates a favorable prognosis for an uncomplicated course during pregnancy and a live birth, even in individuals with severe histopathologic changes by renal biopsy and heavy proteinuria in the early stage of their disease. Continued signs of disease activity or renal disease reduce, however, the likelihood for an uncomplicated pregnancy, although persistent proteinuria alone may not represent more of a risk factor than it does in other types of renal disease. The incidence of exacerbation in the present series was not greater postpartum than during pregnancy, as suggested in previous reports. These data indicate, therefore, that generalized conclusions about the prospects of pregnancy should not be made in patients with SLE without consid-

eration of individual features of disease activity and the risk factors suggested by this study.

Acknowledgments

This study was made possible because of the generous contribution of time and effort by individuals in the following institutions: Dr. C. Hong, Backus Hospital, Norwich, Connecticut; Dr. W. N. Suki, Baylor University School of Medicine, Houston, Texas; Drs. A. I. Katz and M. D. Lindheimer, University of Chicago School of Medicine, Chicago, Illinois; Dr. J. H. Galla, University of Kentucky Medical Center, Lexington, Kentucky; Dr. C. Coggins, Massachusetts General Hospital, Boston, Massachusetts; Drs. G. Porter and R. Muther, University of Oregon School of Medicine; Drs. T. Hutchinson and D. Bichet, Royal Victoria Hospital, Montreal, Canada; Drs. S. Unterhalter and R. L. Jamison, Stanford University Medical Center, Stanford, California; Dr. J. A. Amato, St. Francis Hospital, Hartford, Connecticut; Dr. M. Forland, University of Texas Health Science Center, San Antonio, Texas; Drs. K. S. Shapiro, S. H. Hou, J. Harrington, J. Gennari, and J. J. Cohen, Tufts University School of Medicine, Boston, Massachusetts; Dr. J. Renda, Waterbury Hospital, Waterbury, Connecticut; and Drs. N. Siegel and J. Kenney, Yale University School of Medicine, New Haven, Connecticut.

Reprint requests to Dr. J. P. Hayslett, Department of Internal Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA

References

1. Friedman EA, Rutherford JW: Pregnancy and lupus erythematosus. *Obstet Gynecol* 8:601–610, 1956
2. Donaldson LB, deAlvarez RR: Further observations on lupus erythematosus associated with pregnancy. *Am J Obstet Gynecol* 83:1461–1473, 1962
3. Dziubinski EH, Winkelmann RK, Wilson RB: Systemic lupus erythematosus and pregnancy. *Am J Obstet Gynecol* 84:1873–1877, 1964
4. Ellis FA, Bereston ES: Lupus erythematosus associated with pregnancy and menopause. *AMA Arch Dermat Syphil* 65:170–176, 1952
5. Estes D, Christian CL: The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 50:85–105, 1971
6. Fairley KF, Whitworth JA, Kincaid-Smith P: Glomerulonephritis and pregnancy, in *Glomerulonephritis*, edited by Kincaid-Smith P, Mathew TH, Becker EL, New York, John Wiley and Sons, 1973, p. 997
7. Murray FA: Lupus erythematosus in pregnancy. *J Obstet Gynec Br Commonw* 65:401–408, 1958
8. Garsenstein M, Pollak VE, Kark RM: Systemic lupus erythematosus and pregnancy. *N Engl J Med* 267:165–169, 1962
9. Zurier RB, Argyros TG, Urman JD, Warren J, Rothfield NF: Systemic lupus erythematosus: Management during pregnancy. *Obstet Gynecol* 51:178–180, 1978
10. Bear R: Pregnancy and lupus nephritis: A detailed report of six cases with a review of the literature. *Obstet Gynecol* 47:715–718, 1976
11. Estes D, Larson DL: Systemic lupus erythematosus and pregnancy. *Clin Obstet Gynecol* 8:307–321, 1965
12. Cohen AS, Reynolds WE, Franklin EC, et al: Preliminary criteria for the classification of systemic lupus erythematosus. *Bull Rheum Dis* 21:643–648, 1971
13. Hecht B. Siegel N, Adler M, Kashgarian M, Hayslett JP: Prognostic indices in lupus nephritis. *Medicine* 55:163–181, 1976
14. Comerford FR, Cohen AS: The nephropathy of systemic lupus erythematosus: An assessment of clinical, light, and electron microscopic criteria. *Medicine* 46:425–436, 1967
15. Chase H: Perinatal mortality: Overview and current trends. *Clinics Perinatol* 1:3–10, 1974
16. Bierman JM, Siegel E, French TE, Simonian K: Analysis of outcome of all pregnancies in a community. *Am J Obstet Gynecol* 91:37–45, 1965
17. Turner SJ, Levine L, Rothman A: Lupus erythematosus and pregnancy. *Am J Obstet Gynecol* 70:102–108, 1955
18. Cox BJ: Disseminated lupus erythematosus in pregnancy. *Obstet Gynecol* 26:511–514, 1965
19. McGee CD, Makowski EL: Systemic lupus erythematosus in pregnancy. *Am J Obstet Gynecol* 107:1008–1012, 1970
20. Ferris TF: Renal disease, in *Medical Complications During Pregnancy*, edited by Burrow GN, Ferris TF, Philadelphia, W.B. Saunders Co, 1975, p. 1
21. Strauch BS, Hayslett JP: Kidney disease and pregnancy. *Br Med J* 4:578–582, 1974
22. Lindheimer MD, Katz A: *Kidney Function in Pregnancy*. Philadelphia, Lea and Febiger, 1977, pp. 161–162
23. Dujovne I, Pollak VE, Pinani CL, et al: The distribution and character of glomerular deposits in systemic lupus erythematosus. *Kidney Int* 2:33–50, 1972
24. Appel GB, Silva FG, Pirani CL, Meltzer JI, Estes D: Renal involvement in systemic lupus erythematosus (SLE). *Medicine* 57:371–410, 1978
25. Penn I, Makowski E, Droegenmueller W, Halgrimson CG, Starzl TE: Parenthood in renal homograft recipients. *JAMA* 216:1755–1761, 1971